PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07C 315/02, 381/14

A1

(11) International Publication Number: WO 94/21603

(43) International Publication Date: 29 September 1994 (29.09.94)

(21) International Application Number: PCT/US93/12444

(22) International Filing Date: 21 December 1993 (21.12.93)

(30) Priority Data:
07/996,342 23 December 1992 (23.12.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US 07/996,342 (CON)
Filed on 23 December 1992 (23.12.92)

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: WEBB, Kevin, Scott [US/US]; 1415 Powder Horn Drive, Phoenixville, PA 19460 (US).

(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: A PROCESS FOR PREPARING SULFONES

(57) Abstract

Certain sulfides can be converted to sulfoxides or sulfones using oxone in 12.5 % aqueous acetone and buffered to pH 7.5 - 8.0 with sodium bicarbonate.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

A PROCESS FOR PREPARING SULFONES

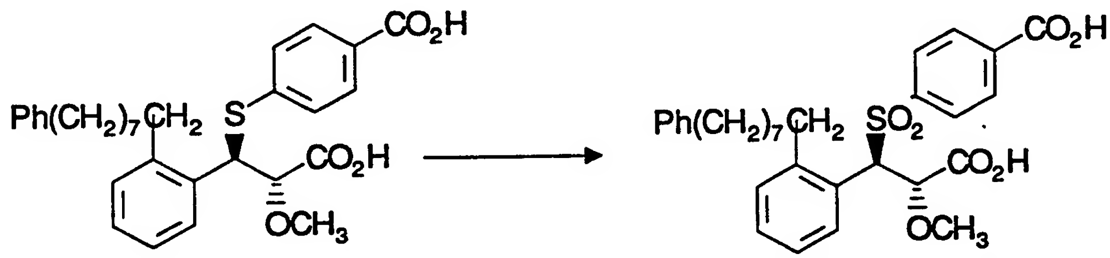
Scope of the Invention

Sulfides have been converted to sulfoxides or sulfones using Oxone® in an water/ketone co-solvent system buffered to pH of about 7.5 - 8.0 with a bicarbonate.

Background

The peptidic leukotrienes LTC_4, LTD_4 and LTE_4 which comprise a special class of arachidonic acid metabolites have been shown to play important roles in cell and tissue biology. In particular, these leukotrienes (C_4, D_4 and E_4) are now believed to be directly involved in a variety of immediate hypersensitivity diseases, among these allergic asthma. A new peptidoleukotriene receptor antagonist, (R*,S*)-β-[(4-carboxyphenyl)sulfonyl)-α–methoxy-2-(8-phenyloctyl)benzene propanoic acid has been discovered and subsequently chosen as a candidate for the treatment of bronchial asthma. This compound and how to make it is disclosed in European Patent Application No. 90306438.4 published where the sulfide was first made, then treated with *m*-perchlorobenzoic acid to obtain the sulfone. The reaction is illustrated in Scheme I.

Scheme I



Synthetic scale-up for new drug testing efforts lead to a search for new methods for oxidizing the sulfide to the sulfone. Although many chemical reagents are known in the literature for this type of oxidation, each appeared unacceptable for the synthesis of kilogram quantities of compounds of this general structural type. What was needed was an oxidation which was amenable to scale-up, operationally simple to perform, and environmentally sound.

Several oxidation procedures were investigated in hopes of finding the optimal conditions for this class of compounds. The following approaches were investigated:

The use of sodium tungstate dihydrate in the presence of 30% hydrogen peroxide was attempted. It gave a mixture of sulfoxide and sulfone (3:1) and prolonged heating (60° C) (insert reference) produced a major undesired impurity as evident by HPLC (25% (PAR)). Alternately, Ammonium molybdate (VI) tetrahydrate and 30% hydrogen peroxide [Amarel, M.J. *J. Chem. Soc.* (c) 1969, 2495] was found to be a rather sluggish reaction. After 96 hours at ambient temperature the reaction was incomplete with 16% of the intermediate sulfoxide remaining. This same reaction at elevated temperatures was unsuccessful, the desired product was found to be unstable to the reaction conditions.

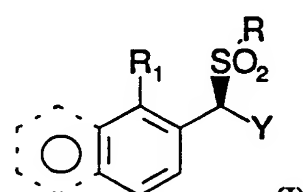
Sodium perborate in glacial acetic acid (McKillop, A.; Tarbin, J.A. *Tetrahedron Lett. 1983, 24(14), 1505.)* proved to be an effective and useful procedure for synthesizing small quantities of the sulfone. However, the physical properties of the drug substance rendered the use of sodium perborate in glacial acetic acid unacceptable for kilogram conversions. Several permutations on the reaction conditions were investigated in hopes of obtaining a workable and reliable procedure, but the replacement of acetic acid by formic acid (88% or 96%) or by 50% aqueous methanol (under acid catalyst) were ineffective in producing a clean conversion of sulfide to sulfone.

Oxone® in 50% aqueous methanol [Trost, B.M.; Curran, D.P. *Tetrahedron Lett. 1990, 31(26), 3685*] or 50 % aqueous acetone [Volkmann, R.A.; Kelbaugh, P.R.; Nason, D.M.; Jasys, V.J. *J. Org. Chem. 1992, 57, 4352*] has been used for sulfide oxidations, but was not a useful procedure for the oxidation of the sulfone of interest here. A phase transfer catalyst, gentle heating (55° C) and excess oxidant were required to produce the desired sulfone in only 65 to 70% isolated yields of inconsistent purity. The use of tetra-*n*-butylammonium oxone (Trost, M.M.; Braslau, R. *J. Org. Chem.* 1988, 53,532) was deemed impractical due to the large amount of solids needed to produce this salt.

Attempts to find a process which would provide a salt form acceptable to regulatory agencies, led to the finding that a carbonate buffered aqueous system using a co-solvent provided great success. The results were an oxone-based oxidation system using a carbonate to buffer the pH and a ketone as the co-solvent. No epimerization was observed under the reaction conditions, and also no elimination of the sulfonyl acid moiety leading to cinnamic acid derivatives occurred.

Summary of the Invention

A process for preparing a sulfone of formula I:



(I)

where the dotted lines indicate a second aromatic ring forming naphthyl may be present,

R_1 is C_8 to C_{13}-alkyl, C_7 to C_{12}-alkoxy, unsubstituted or substituted phenyl-C_4 to C_{10}-alkyl, unsubstituted or substituted phenyl-C_3 to C_9-alkoxy with substituted phenyl is substituted with bromo, chloro, trifluoromethyl, or C_1 to C_4-alkoxy

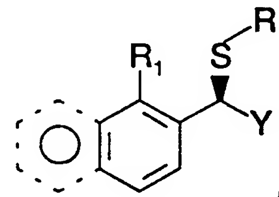
R is $-(CH_2)_nArA$ or ArA where n is 0-6, Ar is phenyl or substituted phenyl, and A is $-(CH_2)_nR_2$, where n is 0-6.

R_2 is -COOH or CO_2X where X is an alkali metal cation,

Y is R_2 or $-CH(R_3)(CH_2)_mR_2$; and

R_3 is hydrogen, methyl, C_1 to C_4 alkoxy, fluoro or hydroxy; wherein the process comprises

i. preparing an aqueous alkali metal salt solution of an acid of formula A;



(A)

ii. buffering said solution to a pH of between 7 - 8.5 using an alkali metal bicarbonate;

iii. adding a ketone co-solvent in an amount between 10 and 15% by volume relative to the water;

iv. adding between 1 and 1.5 equivalents of Oxone®; and

v. running the reaction for between 30 minutes and 2 hours at a temperature between 10° and 50° C.

In formula I and formula A, either the phenyl or naphthyl group can be present. Naphthyl is represented by the use of a dotted outline with a circle in the center; that portion of formulas I and A may be absent, giving the phenyl or may be present giving the naphthyl radical. This invention is intended to cover both sets of compounds.

The sulfides of formula A can be found in the literature, particularly in the patent literature. Compounds where R is an alkyl acid are disclosed in U.S. patent numbers 4,820,719 and 4,874,792. Formula A compounds where R is a 5-membered heterocyclic ring group are disclosed in U.S. patent number 5,135,938. Sulfides where R is a six-membered aryl or heteroaryl group are disclosed in European Patent Application No. 90306438.4. Compounds where the dotted lines denotes naphthyl can be found in European Patent Application 91908637.1. All are incorporated herein by reference in full as if set out here.

The compound of most interest in this invention is that one where R is the 4-carboxyphenyl group. How to make these sulfides is disclosed in European Patent Application 91908637.1. The oxidation of most interest here is that of converting the sulfide (R*,S*)-β[(4-carboxyphenyl)thio)-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid to its corresponding sulfone, the (R*,S*)-β–[(4–carboxyphenyl)sulfonyl)-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid. Both of these compounds are disclosed in EP application 91908637.1. In that application the sulfone was prepared by treating the sulfide with about two equivalents of *m*-perchlorobenzoic acid.

In this process, an aqueous solution of the sulfide in the form of an alkali metal salt is first prepared. This can be done by simply dissolving an existing alkali metal salt in water or by dissolving the free acid in a solution of an alkali metal base, eg. an alkali metal hydroxide.

If the free acid is being dissolved in base, at minimum two equivalents of base should be used. It is preferable to use at least one equivalent of base per acidic function in the molecule, an excess of base is preferred so that complete ionization of all acid groups is achieved. As the cation, the preferred ion is sodium. Sodium hydroxide is the preferred alkali metal hydroxide.

Next a buffering agent is added to adjust the pH. A bicarbonate ion is preferred, particularly the bicarbonate which has the same cation as that of the sulfide salt. Herein sodium bicarbonate is preferred. Bicarbonate is added in an amount sufficient to buffer the solution to a pH between about 7.0 and 8.5, preferably 7.5 to 8.0.

A co-solvent in the form of a water-miscible ketone is then added in an amount between 10 and 15%. Simple ketones such as dimethyl or diethyl ketone may be used. The preferred ketone is acetone. A preferred amount is that of about 12.5%. These figures are measured on a volume/volume basis.

Oxone® (potassium peroxymonosulfate) is then added. This oxidant is commercially available from several suppliers, for example Aldrich Chemical Company, U.S.A. An excess of Oxone® is added. Preferably that excess will be in the range of 1.1 to 1.5 equivalents, though it will be appreciated that an amount exceeding 1.5 equivalents could be used though such added quantities likely would not achieve much in the way of a cost effective transformation of the sulfide to the sulfone. An optimized quantity is believed to be about 1.35 equivalent of Oxone®.

One of the attributes of this improved process is that an elevated temperature is not required to effect the reaction. The reaction can be carried out at ambient temperature or thereabouts. An effective range is anywhere from about 10°C to 50° C. While temperatures in excess of 50°C could be used, there is no perceived benefit in doing so, given that the reaction proceeds to completion with very high yields at ambient temperature in 1 to 2 hours.

In each of the foregoing steps, some form of mixing or stirring can be used as part of the process of carrying out this invention.

After the period allowed for the reaction to go to completion, which can be monitored by some means such as by chromotography, the reaction can be quenched by adding a reducing agent, eg. sodium bisulfite, and the sulfone recovered as the salt. Alternatively, after the reaction is quenched, the solution can be made acidic and by that means the free acid formed; it may be then recovered by any means desired.

The following example is provided to illustrate the invention. It is not indented to limit the invention in any manner. Reference is made to the claims for what is reserved to the inventor.

Examples

Example 1

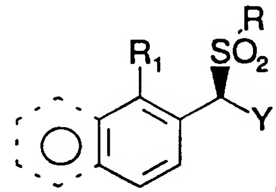
Preparation of (R*,S*)-β-[(4-carboxyphenyl)sulfonyl-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid

To a 500 mL round bottom flask equipped with a magnetic stir bar was charged 1.67 g of sodium hydroxide and 30 mL of dionized water. To the vigorously stirred basic solution was added 9.5 g of (R*,S*)-β-[(4-carboxyphenyl)thio)-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid. The suspension was vigorously stirred at ambient temperature for 20 minutes producing a light yellow solution. To this was added 12.50 g of sodium bicarbonate and 10 mL of acetone. The Oxone® solution (15.00 g in 40 mL of $4X10^{-4}$M EDTA) was quickly added over 5 minutes. The resulting suspension was vigorously stirred for 1/2 hour at ambient temperature. A sample was removed and analyzed by HPLC. The reaction was quenched with sodium bisulfite (9.20 g in 18 mL of deionized water) and stirred for 15 minutes. To the solution was charged 200 mL of ethyl acetate and acidified to pH 2 with 35 mL of 6N (aq) HCl. The organic layers were combined and washed 2 X 75 mL with deionized water, 1 X 75 mL with brine, dried over anhydrous NA_2SO_4, filtered and concentrated via rotovap. The thick oil was placed on the vacuum pump (0.5 torr) for 48 hours and heated to 60° C to give 9.44 grams (94.07%) of the captioned product.

This same process can be used to oxidize any of the sulfides of formula A to the sulfones of formula I.

What is claimed is:

1. A process for preparing a sulfone of formula I:



(I)

where the dotted lines indicate a second aromatic ring forming naphthyl,

R_1 is C_8 to C_{13}-alkyl, C_7 to C_{12}-alkoxy, unsubstituted or substituted phenyl-C_4 to C_{10}-alkyl, unsubstituted with bromo, chloro, trifluoromethyl, or C_1 to C_4-alkoxy

R is $-(CH_2)_nA$, $-(CH_2)_nArA$ where n is 0-6, Ar is phenyl or substituted phenyl, and A is $-(CH_2)_nR_2$, where n is 0-6.

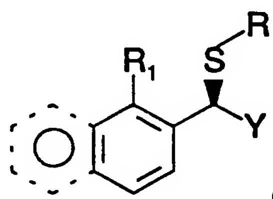
R_2 is -COOH or CO_2X where X is an alkali metal cation,

Y is R_2 or $-CH(R_3)(CH_2)_mR_2$; and

R_3 is hydrogen, methyl, C_1 to C_4 alkoxy, fluoro or hydroxy;

wherein the improvement comprises:

i. preparing an aqueous alkali metal salt solution of an acid of formula A;



(A)

ii. buffering said solution to a pH of between 7 - 8.5 using an alkali metal bicarbonate;

iii. adding a ketone co-solvent in an amount between 10 and 15% by volume relative to the water;

iv. adding between 1 and 1.5 equivalents of Oxone®; and

v. running the reaction for between 30 minutes and 2 hours at a temperature between 10° C and 50° C.

2. The process of claim 1 where the alkali metal hydroxide is NaOH.

3. The process of claim 3 where the alkali metal bicarbonate is sodium bicarbonate and the pH range is 7.5 - 8.0.

4. The process of claim 2 where the ketone is acetone.

5. The process of claim 4 where the sulfide of formula I has a phenyl group and R is 4-carboxyphenyl.

6. The process of claim 5 for oxidizing the sulfide (R*,S*)-β-[(4-carboxyphenyl)thio)-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid, to the sulfone (R*,S*)-β-[(4-carboxyphenyl)sulfonyl)-α-methoxy-2-(8-phenyloctyl)benzene propanoic acid, which process comprises:

i. dissolving the sulfide dissolved in water containing 2.1 equivalents of NaOH,

ii. adding an excess of sodium bicarbonate,

iii. adding acetone in an amount sufficient to make 12.5% acetone/water solution (volume/volume),

iv. adding 1.35 equivalents of Oxone®, and

v. stirring said mixture for 1 hour at ambient temperature.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12444

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 315/02, 381/14
US CL :562/426, 427, 429, 431, 432
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 562/426, 427, 429, 431, 432

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, A, 0,403,249 (FRAZEE ET AL) 19 DECEMBER 1990, see entire document.	1-6
Y	Tetrahedron Letters, Vol. 31, No. 26, issued 1990, Quallich et al, "Diastereoselective Oxidation of Sulfides to Sulfoxides with Potassium Peroxymonosulfate", pgs. 3685-3686; see entire document.	1-6
Y	Journal of Organic Chemistry, Vol. 57, isued 1992, Volkmann et al, "2 Thioalkyl Penems: An Efficient Synthesis of Sulopenem, a (5R.6s)-6(1(R)-Hydroxyethyl)-2-[(cis-1-oxo-3-thiolanyl)thio]-2- penem Antibacterial", pages 4352-4361, see entire document.	1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 FEBRUARY 1994	MAR 15 1994

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MARGARET J. PAGE jd
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12444

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Tetrahedron Letters, Vol. 22, No. 14, issued 1981, Trost et al., "Chemoselective Oxidation of Sulfides to Sulfones with Potassium Hydrogen Persulfate", pages 1287-1290.	1-6